JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Antibiotic resistance before, during, and after the COVID-19 pandemic: a retrospective study

Hadi Al Sulayyim[1,2], Rohani Ismail[1], Abdullah Al Hamid[3], Bazuqamah Mohammed[4], Noraini Abdul Ghafar[5]

[1] Interdisciplinary Health Unit, School of Health Science, Universiti Sains Malaysia (Health Campus), Kubang Kerian 11800, Kelantan, Malaysia
[2] Saudi Ministry of Health, Najran 11134, Saudi Arabia
[3] College of Clinical Pharmacy, Department of Pharmacy Practice, King Faisal University, AlAhsa, Saudi Arabia
[4] Department of Microbiology, King Khalid Hospital, Najran Health Affairs, Najran 11134, Saudi Arabia
[5] Biomedicine Program, School of Health Science, Universiti Sains Malaysia (Health Campus), Kubang Kerian 11800, Kelantan, Malaysia

Abstract

Introduction: Prevalence of antibiotic resistance (AR) during the coronavirus 2019 (COVID-19) pandemic was higher than pre-pandemic times. This study determined the prevalence and patterns of AR among Gram-positive and negative bacteria before, during and after COVID-19 in Saudi Arabia and identified the associated factors.

Methodology: A retrospective cross-sectional study was employed to identify patients with positive AR bacteria between March 2019 and March 2022. The bacterial isolates and patients' data were identified from laboratory and medical records departments retrospectively. Binary logistic regression analysis was performed to identify the factors associated with AR and deaths. Multinominal logistic regression was applied to confirm the factors associated with AR classification.

Results: AR Gram-negative bacteria decreased during and after the pandemic. However, *S. aureus* showed a negligible increase in resistance rate after pandemic, while *E. faecium*, recorded a higher-than-average resistance rate during the pandemic. The prevalence of pan drug resistance (PDR) during the pandemic (85.7%) was higher than before (0%) and after (14.3%), $p = 0.001$. The length of stay and time were significant predictors for AR classification. The odds of multi drug resistance (MDR) development to PDR during the pandemic were 6 times higher than before and after (OR = 6.133, CI =, $p = 0.020$). Age, nationality, COVID-19 infection, smoking, liver disease, and type and number of bacteria were associated with death of patients with positive AR.

Conclusions: Further studies are recommended to explore the prevalence of PDR and to justify the increased rates of *E. faecium* AR during the COVID-19 pandemic.

Key words: antibiotic resistance; COVID-19; pandemic; bacteria; time classification.

J Infect Dev Ctries 2024; 18(3):371-382. doi:10.3855/jidc.19071

(Received 18 August 2023 – Accepted 07 November 2023)

Introduction

Antibiotics are one of the most significant breakthroughs in the medical field. Morbidity and mortality caused by bacterial infections have significantly declined as a result of using antimicrobials [1]. Antimicrobials were first identified by Alexander Fleming in 1928 when he discovered a mold produced by *Penicillium notatum* killing bacteria, mainly *Staphylococcus aureus*. The mold yielded an active agent, which was named penicillin, and considered a natural compound [2]. From that point onwards, an immense number of semisynthetic and synthetic antibiotics have evolved, such as β-lactam antibiotics, aminoglycosides, and quinolones [3,4].

Antibiotic resistance (AR) is defined as the ability of microorganisms such as bacteria to resist antibiotics [5]. Although the period between the 1930s and 1960s was deemed the golden period for the discovery of antibiotics, the misuse of antibiotics resulted in the emergence of AR, which threatened their value [6].

In addition, the lack of development of new drugs due to financial constraints and regulations in the pharmaceutical industry has played a significant role in the slow development of new and effective antibiotics [7]. AR is a serious public health issue worldwide, affecting the health of humans, animals, and environment. Multi drug resistant (MDR) bacteria are the primary reason for this public health issue because

of their emergence, dispersion, and persistence [8]. The interconnectedness between humans, animals, and the environment has led to the effect of AR being shared across species [9].

The COVID-19 pandemic affected almost all nations [10]. In most cases, the majority of the patients received antibiotics which were not prescribed based on microbiological evidence. Approximately 70% of COVID-19 patients were treated with antibiotics or antifungals, and only 10% of them had either bacterial or fungal coinfections [10,11].

AR increased in most countries during the COVID-19 pandemic to levels higher than pre-pandemic levels [12–14]. This was especially the case with Gram-negative bacteria [15].

The factors that contributed to the surge in AR during the pandemic include improper use of antibiotics [16], self-prescription of antibiotics without consulting a physician, overprescription of antibiotics for COVID-19 patients [17,11], lack of antimicrobial stewardship programs (ASP), and lack of awareness of ASP among physicians [18,19]. On the other hand, the implementation of robust infection prevention and control (IPC) guidelines has led to a reduction in methicillin-resistant *S. aureus* and device-associated bloodstream infections [20]. Governmental policies such as social distancing and restriction of hospital visits has resulted in positive consequences [20,21]. Intensifying IPC precautions also has positive consequences in significantly reducing multi drug resistance (MDR) organisms after the pandemic compared to pre-pandemic times [22].

Previous reports on AR and its relation to the COVID-19 pandemic have focused on AR either during or after the COVID-19 pandemic, measuring the impact of COVID-19 on AR over a few months or one year. Therefore, this study aimed to determine AR prevalence before, during and after the pandemic in Saudi Arabia (SA). Further, it identified the patterns of AR among Gram-positive and Gram-negative bacteria before, during, and after COVID-19. Finally, it attempted to assess the factors associated with AR classification and factors associated with the death of patients with positive AR.

Methodology

Study design and settings

A retrospective cross-sectional study was used to analyze the incidence of AR before, during, and after the COVID-19 pandemic at a government hospital with capacity of 300 beds in Najran, SA, using patients' medical records and laboratory findings.

Inclusion criteria and data extraction

Patients with infections caused by AR organisms before, during and after COVID-19 at a governmental hospital in Najran, SA, were included. Patients with no infections by AR organisms before, during and after COVID-19 were excluded.

All bacterial isolates that exhibited AR before, during and after COVID-19 at the governmental hospital in Najran, SA, were included. Bacterial isolates before March 2019 and after March 2022 and isolates with bacteria that were not AR from March 2019 to March 2022 were excluded.

Demographic data, comorbidities, bacterial species, resistance classification, and outcome data were collected in Microsoft Excel and then analyzed with Statistical Package for Social Sciences (SPSS) version 27. Data were collected from 1 August to 15 September 2022.

Study population and sampling technique

In this study, we included all patients who were infected with AR bacteria from March 2019 to March 2022 to be representative for all patients according to the time classification. The total number of included patients was 1399. All AR bacterial isolates from March 2019 to March 2022 were included to identify the type of bacteria and AR according to the time classification. Patients and patterns of AR were classified into three time groups: before, during, and after COVID-19. Overall, 5755 isolates were included, with 2305 isolates before, 1542 during, and 1908 after the pandemic. Duplicated and repeated isolates and contaminated samples were excluded. Only the first isolate was counted.

Identification of bacterial isolates and antibiotic sensitivity testing

The identification of bacterial pathogens in clinical samples was conducted with standard procedures as requested by the treating physician and assessed by microbiologists. Blood agar, chocolate agar and MacConkey agar were used for culturing bacteria from the different specimens, except urine where blood agar and cysteine electrolyte deficient agar were used. In the case of blood culture, blood was collected in Bactec bottles and incubated in Bactec FX machines (Bection-Dickinson, BD, Sparks, MD, USA) for a maximum of 5 days. After bacterial growth was confirmed by the machine, it was further subcultured on blood agar, chocolate agar and MacConkey agar.

The inoculated agar plates were initially incubated at 37 °C for 18 to 24 hours. After the first incubation,

the agar plates were examined and Gram staining of bacterial colonies was performed. Positive bacterial cultures were further processed for bacterial identification and antibiotic sensitivity testing (AST).

The bacterial pathogens were cultured from clinical samples according to standard procedures. Bacterial identification and AST were performed using a BD Phoenix100™ instrument (BD Corporation, Sparks, USA) or VITEK 2 Compact instruments (bioMérieux, Hazelwood, MO, USA). The results of AST were interpreted according to breakpoints established by the Clinical and Laboratory Standards Institute guidelines (CLSI) [23].

The isolated bacteria were categorized into MDR, extensive drug resistance (XDR), and pan drug resistance (PDR) based on their resistance to the routinely tested antibiotics available in our laboratory. We used minimum inhibitory concentration (MIC) methods and automated machines for AST. The BD Phoenix100™ instrument (BD Corporation, Sparks, USA) was used for almost 95% of the cases, while the VITEK 2 Compact Instruments (bioMérieux, Hazelwood, MO, USA) were used for almost 5% of cases.

The antibiotics tested routinely in all Gram-negative organisms were amikacin, gentamicin, ertapenem, imipenem, meropenem, cephalothin, cefuroxime, cefoxitin, ceftazidime, ceftriaxone, cefepime, aztreonam, ampicillin, amoxicillin-clavulanate, piperacillin-tazobactam, colistin, trimeth-sulfamethoxazole, nitrofurantoin, ciprofloxacin, levofloxacin, and tigecycline.

The antibiotics tested routinely in all Gram-positive organisms were gentamicin, imipenem, cefoxitin, cefotaxime, ampicillin, penicillin G, oxacillin, amoxicillin-clavulanate, daptomycin, trimeth-sulfamethoxazole, tetraclanin, vancomycin, clindamycin, erythromycin, fusidic acid, linezolid, high-level marpirocin, nitrofurantoin, ciprofloxacin, moxifloxacin, rifampin, and tetracycline.

Identification of COVID-19 patients

COVID-19 infection was identified by SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT–PCR) test on nasopharyngeal swab samples at the Regional Laboratory in Najran, SA.

Operational definition

MDR was defined as the ability of microorganisms, mainly bacteria, to resist more than three classes of antibiotics. XDR was defined as the resistance of bacteria to all but two or fewer classes of antibiotics. PDR was defined as the resistance of bacteria to all classes of antibiotics [24].

Before COVID-19 referred to the time from March 2019 to March 2020. During COVID-19, referred to the time from March 2020 to March 2021. After COVID-

Table 1. Demographic, clinical, and outcome data of patients who were positive for AR before, during and after COVID-19.

Variable	Categories	Time classification			*p* value
		Before	During	After	
Age	M (SD)	51 (± 25)	57 (± 21)	54 (± 24)	0.001*
Length of Stay	M (SD)	54 (± 111)	39 (± 56)	32 (± 40)	0.002*
No. of associated bacteria	M (SD)	1 (± 1)	1 (± 1)	1 (± 0)	0.001*
Gender	Female	172 (40.2)	117 (27.3)	139 (32.5)	0.952
	Male	392 (40.4)	258 (26.6)	321 (33.1)	
Nationality	Saudi	319 (37.5)	223 (26.2)	309 (36.3)	0.002*
	Non-Saudi	245 (44.7)	152 (27.7)	151 (27.6)	
Location	OPD/ER	21 (23.1)	20 (22)	50 (54.9)	0.002*
	Inpatient	269 (41.9)	149 (23.2)	224 (34.9)	
	ICU	274 (41.1)	206 (30.9)	186 (27.9)	
Smoking	No	558 (40.5)	368 (26.7)	453 (32.8)	0.585
	Yes	6 (30)	7 (35)	7 (35)	
Hypertension	No	403 (44)	221 (24.1)	292 (31.9)	0.001*
	Yes	161 (33.3)	154 (31.9)	168 (34.8)	
Diabetes Mellitus	No	385 (44.6)	184 (21.3)	295 (34.1)	0.001*
	Yes	179 (33.5)	191 (35.7)	165 (30.8)	
Liver Disease	No	551 (40.7)	357 (26.4)	446 (32.9)	0.102*
	Yes	13 (28.9)	18 (40)	14 (31.1)	
Kidney Disease	No	525 (41.1)	335 (26.2)	417 (32.7)	0.115
	Yes	39 (32)	40 (32.8)	43 (35.2)	
AR Class	MDR	547 (40.8)	352 (26.2)	442 (33)	0.001*
	XDR	17 (38.6)	11 (25)	16 (36.4)	
	PDR	0 (0)	12 (85.7)	2 (14.3)	
Outcome	Survived	395 (42)	231 (24.5)	315 (33.5)	0.021*
	Died	169 (36.9)	144 (31.4)	145 (31.7)	

AR: antimicrobial resistance; COVID-19: coronavirus disease 2019; ER: emergency; ICU: intensive care unit; M: mean; MDR: multi drug resistant; OPD: outdoor patient department; PDR: pan drug resistant; SD: standard deviation; XDR: extensive drug resistant. *Significant at $\alpha = 0.05$.

19 referred to the time from March 2021 to March 2022 [25-27].

Statistical analysis

Data were presented as percentage (%) and means (SD). χ^2 test, and one-way ANOVA were used for comparisons. Multinomial logistic regression was applied to confirm the factors associated with AR classification. Binary logistic regression analysis was performed to identify factors associated with AR and death. SPSS version 27 was used to analyze the data.

Ethical approval

Ethical approval for the study was obtained from the Human Research Ethical Committee (HREC) of Universiti Sains Malaysia (USM) (JEPeM Code = USM/JEPeM/22040202) and Institutional Review Board (IRB) at the General Directorate of Health Affairs (IRB Log Number 2022-22f) Najran, SA. As the study was based on the patients' laboratory records, the IRB was ethically sufficient.

Results

Of the 1441 patients with AR bacteria, 42 patients were excluded from the study due to missing data in their medical records. Therefore, 1399 (97.1%) patients were included. Demographic, clinical, and outcome data of patients who were positive for AR bacteria before, during and after COVID-19 are summarized in Table 1. The patients' mean age during the pandemic (57 ± 21 years) was significantly higher compared with that the age before (51 ± 25 years) and after (54 ± 24 years) the COVID-19 pandemic ($p \leq 0.001$). The mean length of stay was higher before the pandemic (54 ± 111 days) than during the pandemic (39 ± 56 days) and after the pandemic ((32 ± 40 days), $p = 0.002$). The number of positively associated AR bacteria after the pandemic was lower than that before and during the pandemic ($p = 0.001$). There were no significant differences in the number of male or female patients or the number of smoker and non-smoker patients, ($p = 0.952$ and $p = 0.585$, respectively). Among Saudi patients, the prevalence of AR during the pandemic was less than that before and after the pandemic. However, among non-Saudi patients, the prevalence of AR was higher before the pandemic than during and after the pandemic ($p = 0.002$). In terms of the types of wards in the hospital, AR cases in the outpatient department (OPD) and emergency (ER) were most prevalent after the pandemic. However, AR cases were most prevalent in the ICU before the pandemic ($p = 0.002$). The prevalence of comorbidities; hypertension, diabetes mellitus, and liver diseases varied over the period of the study ($p = 0.001$, $p = 0.001$, and $p = 0.002$, respectively). PDR was highly prevalent during pandemic: 12 (85.7%) compared to before 0 (0%) and after 2 (14.3%), $p = 0.001$. The percentage of surviving patients was higher before the pandemic than during and after the pandemic ($p = 0.021$).

Table 2 illustrates the association between the selected predictors and AR classification. Approximately 3.3% OPD/ER, 2.3% inpatients, and

Table 2. Assessing the association between selected predictors and AR classification.

Variable	Categories	AR Classification			*p* value
		MDR	XDR	PDR	
Location	OPD/ER	88 (96.7)	3 (3.3)	0 (0)	0.025*
	Inpatient	625 (97.4)	15 (2.3)	2 (0.3)	
	ICU	628 (94.3)	26 (3.9)	12 (1.8)	
Gender	Female	416 (97.2)	11 (2.6)	1 (0.2)	0.111
	Male	925 (95.3)	33 (3.4)	13 (1.3)	
Multiple admission	No	552 (95)	17 (2.9)	12 (2.1)	0.003*
	Yes	789 (96.5)	27 (3.3)	2 (0.2)	
Nationality	Saudi	815 (95.8)	29 (3.4)	7 (0.8)	0.558
	Non-Saudi	526 (96)	15 (2.7)	7 (1.3)	
COVID-19 infection	No	1112 (96)	41 (3.5)	5 (0.4)	0.001*
	Yes	229 (95)	3 (1.2)	9 (3.7)	
Hypertension	No	884 (96.5)	23 (2.5)	9 (1)	0.172
	Yes	457 (94.6)	21 (4.3)	5 (1)	
Diabetes Mellitus	No	831 (96.2)	26 (3)	7 (0.8)	0.613
	Yes	510 (95.3)	18 (3.4)	7 (1.3)	
Liver Disease	No	1297 (95.8)	43 (3.2)	14 (1)	0.737
	Yes	44 (97.8)	1 (2.2)	0 (0)	
Kidney Disease	No	1222 (95.7)	41 (3.2)	14 (1.1)	0.454
	Yes	119 (97.5)	3 (2.5)	0 (0)	
Time classification	Before	547 (97)	17 (3)	0 (0)	0.001*
	During	352 (93.9)	11 (2.9)	12 (3.2)	
	After	442 (96.1)	16 (3.5)	2 (0.4)	

AR: antimicrobial resistance; COVID-19: coronavirus disease; ER: emergency; ICU: intensive care unit; MDR: multi drug resistant; OPD: outdoor patient department; PDR: pan drug resistant; XDR: extensive drug resistant. *Significant at $\alpha = 0.05$.

Table 3. Factors associated with AR classification.

Variable		XDR univariate		XDR multivariate		PDR univariate		PDR multivariate	
		OR (95% CI)	***p value***	**OR (95% CI)**	***p value***	**OR (95% CI)**	***p value***	**OR (95% CI)**	***p value***
Length of stay		1.003 (1.001-1.004)	0.004*	1.003 (1.001-1.005)	0.005*	1.001 (0.995-1.007)	0.826	1.004 (0.994-1.013)	0.429
Time classification	Before	0.859 (0.429-1.719)	0.667	0.668 (0.320-1.394)	0.282	0.865 (0.529-1.829)	0.757	0.579 (0.423-1.484)	0.492
	During	0.863 (0.396-1.884)	0.712	0.968 (0.436-2.149)	0.935	7.534 (1.675-33.883)	0.008*	6.133(1.326-28.374)	0.020*
	After	Ref		Ref		Ref		Ref	

Reference category of AR was MDR. AR: antimicrobial resistance; CI: confidence interval; MDR: multi drug resistant; OR: odds ratio; PDR: pan drug resistant; Ref: reference; XDR: extensive drug resistant; *Significant at α = 0.05.

3.9% ICU patients had XDR compared to 0%, 0.3%, and 1.8% of those who had PDR, respectively (p = 0.025).

The prevalence of XDR was higher than that of PDR among patients with multiple admissions (3.3% vs 0.2%, p = 0.003). The prevalence of PDR among COVID-19 patients was higher than XDR (3.7% vs 1.2%, p = 0.001). The prevalence of XDR before and after the pandemic (3% and 3.5%) was higher than that of PDR (0% and 0.4%), whereas the prevalence of PDR during the pandemic (3.2%) was higher than that of XDR (2.9%), p = 0.001.

Table 3 presents the results of the multinomial logistic regression for factors associated with AR classification. In univariate analysis, length of stay and time classification were statistically significant predictors for AR classification. In the multivariate model, the predictors that were statistically significant were length of stay and time classification.

When comparing XDR with MDR, as the length of stay increased by one day, the multinomial log-odds of MDR development to XDR would be expected to increase by 1.003 units while holding all other variables in the model constant (OR = 1.003, CI = 1.001–1.005, p = 0.005). In the case of PDR relative to MDR, the odds of MDR development to PDR during the COVID-19 pandemic were 6 times higher than the times before and after (OR = 6.133, CI = 1.326–28.374, p = 0.020).

Logistic regression analysis for factors associated with death are presented in Table 4. In univariate analysis, age, nationality, COVID-19 infection, smoking, hypertension, diabetes mellitus, liver disease, kidney disease, bacterial infection, AR type, time classification, and number of associated bacteria were statistically significantly associated with death. In the

Table 4. Logistic regression analysis of factors associated with death.

Variable	**Categories**	**Univariate**		**Multivariate**	
		OR (95% CI)	***p* value**	**OR (95% CI)**	***p* value**
Age		1.029 (1.023-1.034)	0.001*	1.033 (1.026-1.040)	0.001*
Nationality	Saudi	1.928 (1.518-2.449)	0.001*	1.384 (1.037-1.847)	0.027*
	Non-Saudi	Ref		Ref	
COVID-19	Yes	2.964 (2.232-3.936)	0.001*	2.528 (1.780-3.592)	0.001*
	No	Ref		Ref	
Smoking	Yes	3.138(1.274-7.731)	0.013*	3.423 (1.286-9.113)	0.014*
	No	Ref		Ref	
Hypertension	Yes	1.906 (1.512-2.402)	0.001*	0.882 (0.636-1.223)	0.451
	No	Ref		Ref	
Diabetes mellitus	Yes	1.764 (1.405-2.215)	0.001*	0.841 (0.618-1.144)	0.271
	No	Ref		Ref	
Liver disease	Yes	3.212 (1.750-5.896)	0.001*	5.017 (2.483-10.140)	0.001*
	No	Ref		Ref	
Kidney disease	Yes	1.654 (1.135-2.411)	0.009*	1.403 (0.911-2.160	0.125
	No			Ref	
Type of bacteria	*E. faecium*	0.946 (0.258-3.467)	0.934	0.361 (0.090-1.1441)	0.149
	A. baumannii	3.062 (2.032-4.614)	0.001*	2.754 (1.745-4.346)	0.001*
	P. aeruginosa	2.617 (1.279-5.358)	0.008*	0.410 (0.053-3.198)	0.395
	E. Coli	1.230 (0.792-1.911)	0.356	0.780 (0.482-1.264)	0.314
	K. pneumonia	3.176 (2.091-4.823)	0.001*	2.057 (1.298-3.258)	0.002*
	S. aureus	Ref		Ref	
AR classification	XDR	1.452 (0.787-2.677)	0.232	5.056 (0.730-35.016)	0.101
	PDR	2.097	0.168	1.328 (0.423-4.166)	0.627
	MDR	Ref		Ref	
Time classification	During	1.457 (1.106-1.919)	0.007*	0.882 (0.622-1.250)	0.48
	After	1.076 (0.824-1.405)	0.591	0.851 (0.616-1.175)	0.327
	Before	Ref		Ref	
No of associated Bacteria		1.486 (1.248-1.770)	0.001*	1.433 (1.157-1.774)	0.001*

CI: confidence interval; COVID-19: coronavirus disease 2019; MDR: multi drug resistant; OR: odds ratio; PDR: pan drug resistant; Ref: reference; XDR: extensive drug resistant. *Significant at α = 0.05.

multivariate model, factors that were independently significantly associated with death were age (p = 0.001), nationality (p = 0.027), COVID-19 infection (p = 0.001), smoking (p = 0.014), liver disease (p = 0.001), type of bacteria and number of associated bacteria (p = 0.001). As the age increased by one year, the risk of death of patients with positive AR increased by 3% (B = 1.033, CI = 1.026–1.040, p = 0.001). Compared with non-Saudi patients, the odds of death among Saudi patients who had positive AR bacteria was 1.4 times higher (B = 1.384, CI = 1.037–1.847, p = 0.027). The odds of death of patients who had positive AR infection by COVID-19 was 2.5 times higher than those who had no COVID-19 infection (B = 2.528, CI = 1.780–3.592, p = 0.001). Compared with non-smoker-positive AR patients, the odds of death among patients who were smokers was 3.4 times higher (B = 3.423, CI = 1.286-9.113, p = 0.014). The odds of death among patients with positive AR bacteria who had liver disease were 5 times higher than those among patients who had no liver disease (B = 5.017, CI = 2.483–10.140, p = 0.001). Patients infected with AR *Acinetobacter baumannii* (B = 2.754, CI = 1.745–4.346, p = 0.001) and *Klebsiella pneumoniae* (B = 2.075, CI = 1.298–3.258, p = 0.002) were more likely to die than patients who had AR *S. aureus*. As the number of positively associated bacteria during the same admission increased by one organism, the death of positive AR patients increased by 43% (B = 1.433, CI = 1.157–1.774, p = 0.001).

The susceptibility of Gram-positive and Gram-negative bacteria before, during, and after the COVID-19 pandemic was obtained from the database of the microbiological laboratory. The total number of AR isolates of the common bacteria included in this study was 5755. This could be further divided into 2305 isolates before the pandemic, 1542 during the pandemic, and 1908 after the pandemic.

The AR of predominant Gram-positive bacteria (*S. aureus*, *Enterococcus faecium*) before, during, and after the COVID-19 pandemic is presented in Table 5. *S. aureus* showed negligible resistance rates after COVID-19 to most tested antibiotics, such as oxacillin (7%), linezolid (2%), teicoplanin (3%), clindamycin (4%), and imipenem (7%), $p \geq 0.05$, whereas resistance to moxifloxacin (24%) was statistically significant ($p \leq 0.05$). Notably, during the COVID-19 pandemic, there was a reduction in *S. aureus* resistance to the majority of antibiotics compared to before and after the COVID-19 pandemic. Interestingly, *S. aureu*s showed 0% resistance against daptomycin and vancomycin before, during, and after the pandemic.

The resistance of *E. faecium* to ampicillin fluctuated, and daptomycin increased by 7%; however, this increase was not statistically significant. Notably, the resistance of *E. faecium* to the tested antibiotics after COVID-19 had decreased. During the pandemic, there was a high level resistance in *E. faecium* to ciprofloxacin (13%), linezolid (34%), teicoplanin (22%), tetracycline (32%), and vancomycin (20%), when compared with before and after the pandemic (p value ≤ 0.05) (Table 5).

The AR pattern of Gram-negative bacteria (*A. baumannii*, *Pseudomonas aeruginosa*, *Escherichia. coli*, *K. pneumonia*) before, during, and after COVID-19 is presented in Table 6. Although *A. baumannii* had gradually increasing resistance to amikacin over the three years from 66% to 82% (p = 0.019), there was a reduction in resistance to the other tested antibiotics, where levofloxacin dropped significantly from 97% to 88%, p = 0.046, and trimethoprim/sulfamethoxazole

Table 5. AR pattern of predominant Gram-positive bacteria before, during, after COVID-19 pandemic.

Antibiotic		*S. aureus*				*E. faecium*			
		Before 535	**During 379**	**After 379**	***p* value**	**Before 38**	**During 33**	**After 53**	***p* value**
Amoxicillin_Clavulanate	R: N (%)	241 (45)	140 (37)	193 (51)	0.135	-	-	-	
Ampicillin	R: N (%)	-	-	-		28 (75)	26 (79)	41 (77)	0.866
Cefotaxime	R: N (%)	241 (45)	136 (36)	197 (52)	0.074	-	-	-	
Ciprofloxacin	R: N (%)	118 (22)	91 (24)	95 (25)	0.879	31 (82)	31 (95)	37 (70)	**0.024***
Clindamycin	R: N (%)	75 (14)	49 (13)	68 (18)	0.578	-	-	-	
Daptomycin	R: N (%)	0	0	0	1	0	1 (3)	4 (7)	0.185
Erythromycin	R: N (%)	139 (26)	106 (28)	133 (35)	0.343	32 (84)	29 (88)	50 (94)	0.072
Gentamicin	R: N (%)	48 (9)	19 (5)	30 (8)	0.529	-	-	-	
Imipenem	R: N (%)	241 (45)	140 (37)	197 (52)	0.102	-	-	-	
Linezolid	R: N (%)	0	0	8 (2)	0.134	0	11 (33)	8(15)	**0.001***
Moxifloxacin	R: N (%)	0	15 (4)	91 (24)	**0.003***	-	-	-	
Nitrofurantoin	R: N (%)	0	0	4 (1)	0.367	36 (96)	29 (89)	44 (83)	**0.011***
Oxacillin	R: N (%)	241 (45)	136 (36)	197 (52)	0.074	-	-	-	
Rifampin	R: N (%)	11 (2)	4 (1)	11 (3)	0.6	13	42	-	
Teicoplanin	R: N (%)	0	8 (2)	11 (3)	0.241	14 (37)	19 (59)	17 (33)	**0.001***
Tetracycline	R: N (%)	91 (17)	45 (12)	42 (11)	0.409	8 (21)	17 (53)	23 (43)	**0.001***
Vancomycin	R: N (%)	0	0	0	1	14 (37)	19 (57)	20 (37)	**0.004***

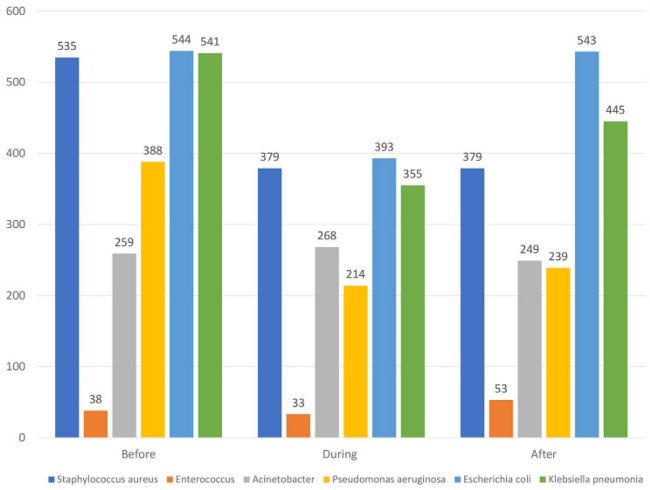
AR: antimicrobial resistance; COVID-19: coronavirus disease 2019; N: number; R: resistance; %: percentage. *Significant at α = 0.05.

increased insignificantly during and after COVID-19 by 7%, $p = 0.401$. Likewise, the resistance patterns of *P. aeruginosa*, *E. coli*, and *K. pneumonia* to the tested antibiotics decreased over three years; for example, the resistance of *P. aeruginosa* to cefepime and ceftazidime was significantly decreased by 15% ($p = 0.049$). The resistance of *E. coli* to amoxicillin-clavulanate, cefepime, and ceftazidime also dropped significantly ($p \leq 0.05$), and the resistance of *K. pneumonia* to gentamycin, piperacillin/tazobactam, and nitrofurantoin declined significantly ($p < 0.05$).

Interestingly, the resistance of *E. coli* to amikacin (1%) and tigecycline (2%) remained steady before, during, and after COVID-19. Likewise, although the resistance of *K. pneumonia* to amikacin during COVID-19 was 43%, the values were the same at 32% before and after COVID-19 (Table 6).

Before the COVID-19 pandemic, the most predominant AR bacteria were *E. coli* (544), followed by *K. pneumonia* (541) and *S. aureus* (535). During COVID-19, *E. coli* was the predominant AR bacteria (393), followed by *S. aureus* (379) and *K. pneumonia* (355). After COVID-19, *E. coli* continued to be the most common AR bacteria (543), followed by *K. pneumonia* (445) and *S. aureus* (379) (Figure 1).

Figure 1. Most predominant antimicrobial resistance (AR) bacteria before, during, and after COVID-19 pandemic.



Discussion

To the best of our knowledge, this is the first study assessing AR before, during, and after the COVID-19 pandemic over three consecutive years. The prevalence of PDR among COVID-19-positive patients during the pandemic was high compared to XDR. The length of stay and time classification were significant predictors for AR classification. The factors associated with death were age, nationality, COVID-19 infection, smoking, liver disease, type of bacteria, and number of associated bacteria. *S. aureus* showed negligible resistance after the pandemic, which could be due to resuming routine work, such as reopening OPD and elective surgery, and *E. faecium* exhibited high resistance during the pandemic, which could be due to ICU admission, devices (such as catheters and ventilators), prophylactic antibiotics, and immunosuppression [28-31]. However, the resistance of Gram-negative bacteria decreased during and after the pandemic compared to before the pandemic. The predominance of AR bacteria did not change substantially.

In a study evaluating bacterial agents before and after COVID-19, there was no difference in terms of age and gender before and after the pandemic [32]. In our study, the patients' mean age during the pandemic was significantly higher than that before and after the

Table 6. AR pattern of predominant Gram-negative bacteria before, during, after COVID-19 pandemic.

Antibiotic		*A. baumannii*				*P. aeruginosa*				*E. coli*				*K. pneumonia*			
		Before N (259)	During N (268)	After N (249)	*p* value	Before N (388)	During N (214)	After N (239)	*p* value	Before N (544)	During N (393)	After N (543)	*p* value	Before N (541)	During N (355)	After N (445)	*p* value
Amikacin	R N (%)	171 (66)	179 (67)	203 (82)	**0.019***	43 (11)	19 (9)	22 (9)	0.87	5 (1)	4 (1)	5 (1)	0.999	173 (32)	121 (34)	142 (32)	0.941
AMC	R N (%)	-	-	-		-	-	-	-	272 (50)	161 (41)	168 (31)	0.001*	379 (70)	217 (61)	245 (55)	0.088
Ampicillin	R N (%)	-	-	-		-	-	-	-	473 (87)	314 (80)	418 (77)	0.176	-	-	-	
Aztreonam	R N (%)	-	-	-		186 (48)	88 (41)	88 (37)	0.28	321 (59)	193 (49)	233 (43)	0.073	384 (71)	220 (62)	276 (62)	0.305
Cefepime	R N (%)	235 (91)	239 (89)	213 (85)	0.404	140 (36)	71 (33)	50 (21)	0.05*	321 (59)	193 (49)	212 (39)	**0.018***	390 (72)	227 (64)	254 (57)	0.086
Cefoxitin	R N (%)	-	-	-		-	-	-		82 (15)	55 (14)	71 (13)	0.92	325 (60)	185 (52)	236 (53)	0.464
Ceftazidime	R N (%)	236 (91)	242 (89)	225 (85)	1	132 (36)	64 (33)	62 (21)	**0.049***	316 (59)	193 (49)	255 (39)	**0.018***	390 (72)	224 (64)	258 (57)	0.086
Ceftriaxone	R N (%)	245 (95)	299 (86)	225 (90)	0.341	0 (0)	0 (0)	0 (0)		326 (60)	200 (51)	244 (45)	0.102	390 (72)	227 (64)	263 (59)	0.151
Cefuroxime	R N (%)	-	-	-		-	-	-		354 (65)	216 (55)	272 (50)	**0.017***	411 (76)	234 (66)	276 (62)	0.092
Imipenem	R N (%)	251 (97)	241 (90)	224 (90)	**0.01***	186 (48)	88 (41)	84 (35)	0.175	49 (9)	31 (8)	33 (6)	0.719	298 (55)	181 (51)	187 (42)	0.169
Meropenem	R N (%)	250 (97)	241 (90)	222 (90)	0.076	155 (48)	64 (41)	65 (35)	0.175	27 (9)	24 (8)	22 (6)	0.81	271 (55)	174 (51)	187 (42)	0.169
Ertapenem	R N (%)	-	-	-		-	-	-		27 (5)	24 (6)	22 (4)	0.779	319 (59)	192 (54)	209 (47)	0.232
Gentamicin	R N (%)	227 (88)	232 (86)	226 (91)	1	116 (30)	60 (28)	53 (22)	0.412	131 (24)	83 (21)	92 (17)	0.471	314 (58)	167 (47)	187 (42)	**0.047***
Nitrofurantoin	R N (%)	-	-	-		-	-	-	-	44 (8)	31 (8)	16 (3)	0.245	390 (72)	234 (66)	227 (51)	**0.007***
Pip-tazo	R N (%)	252 (97)	245 (90)	225 (90)	0.121	116 (48)	62 (41)	50 (35)	0.175	98 (9)	47 (8)	38 (6)	0.719	341 (55)	195 (51)	209 (42)	**0.026***
TMP-SMX	R N (%)	186 (72)	211 (79)	196 (79)	0.401	0 (0)	0 (0)	0 (0)		294 (54)	204 (52)	266 (49)	0.776	303 (56)	167 (47)	218 (49)	0.123
Tigecycline	R N (%)	-	-	-		-	-	-		11 (2)	8 (2)	11 (2)	1	162 (30)	78 (22)	102 (23)	0.363
Ciprofloxacin	R N (%)	252 (97)	246 (92)	222 (89)	0.09	155 (40)	71 (33)	67 (28)	0.197	-	-	-		-	-	-	
Levofloxacin	R N (%)	251 (97)	238 (89)	220 (88)	**0.046***	175 (45)	81 (38)	79 (33)	0.196	-	-	-		-	-	-	

AMC: amoxicillin/clavulanate; AR: antimicrobial resistance; COVID-19: coronavirus disease 2019; N: number; Pip/Tazo: piperacillin/tazobactam; R: resistance; TMP/SMX: trimethoprim/sulfamethoxazole; %: percentage. *Significant at $\alpha = 0.05$.

pandemic ($p \leq 0.001$). There was no significant difference in the gender of patients in the present study before, during, and after the pandemic, which is similar to the observations of Bahce *et al*. [32]. In contrast, in India, there was a significant difference in terms of the gender of patients with positive AR before and during the pandemic [33]. In addition, Bahce *et al.* stated that the mean hospitalization period before the pandemic was 33.59 days and after the pandemic was 13.49 days, and the mortality rate before the pandemic was 83.6% and after the pandemic was 94% [32]. Similarly, our study found that the mean length of stay was higher before the pandemic (54 days) than during (39 days) and after the pandemic (32 days) ($p = 0.002$), and the percentage of surviving patients was higher before the pandemic than during and after the pandemic ($p = 0.021$). The most prevalent AR cases in the present study were from OPD/ER after the pandemic, while there were more cases from wards and the ICU before the pandemic ($p = 0.002$). Unlike the observations of Vikas *et al.,* there were more AR cases in the ICU during the pandemic, while before the pandemic, the cases were higher in the wards [33]. In our study, PDR was highly prevalent during the pandemic (85.7%) compared to before 0% and after 14.3% ($p = 0.001$). This high percentage of PDR during COVID-19 could be explained by overuse of antibiotics, increased length of stay, and almost no ASP implementation. Comparably, Aldhwaihi *et al*. reported that the prevalence of PDR before the pandemic was 17%, and after the pandemic it was 83% [34].

There is evidence suggesting that the production of adulterated antibiotics, international travel, financial constraints in healthcare, misuse of antibiotics either in agriculture or by humans, and climate change are interrelated determinants of AR [35]. AR (MDR) infections were associated with the length of stay in the hospital, particularly in the ICU; however, they were not associated with a high risk of death [36]. A systematic review identified self-medication and prescribing antibiotics by general practitioners as risk factors of AR during the pandemic [14]. In the present study, length of stay and time classification were the predictors associated with AR classification.

In our study, the factors associated with death of patients with positive AR before, during, and after the pandemic were age, nationality, COVID-19 infection, smoking, liver disease, type of bacteria, and number of associated bacteria. Some of these factors, such as, COVID-19, smoking, and number of associated bacteria, were not reported previously; however, previous studies have reported old age, chronic liver disease, and bacterial infection (*E. coli, K. pneumonia, A. baumanii*) as factors associated with death of patients with positive AR [37-40]. In contrast, chronic renal diseases, ICU admission, inability to perform self-care, chronic lung diseases, occupation, septic shock, hypertension, improper use of empirical antibiotics, and body mass index were risk factors reported in some studies [37,39,41-43].

It is vital to ensure that the use of antibiotics, especially in the ICU, is controlled with prescriptions, to ensure the quality of provided care, hospital stay, infection control, and cost reduction requirements [44-46]. AR had reduced during the pandemic owing to government policies with respect to social distance, restriction of hospital visits involving inpatients and outpatients, and robust IPC practices in communities and healthcare facilities [20].

This study demonstrated an overall reduction in AR among Gram-negative and some Gram-positive bacteria (*S. aureus*) as the direct consequence of the implementation of policies by the IPC and government. Health care workers complied with IPC precautionary measures such as personal protective equipment, surgical or N-95 masks, frequent hand hygiene, and routine surface disinfection. In addition, the observed changes in AR in *S. aureus* after COVID-19 in the present study could be explained by the strict IPC measures, virtual clinics, and rescheduled elective surgeries.

During the pandemic, the hospital was a tertiary and referral center in the region. Therefore, while the hospital was busy with COVID-19 cases, IPC precautionary measures were strictly implemented, outpatient departments were closed, patients met their physicians online, and elective surgeries were rescheduled. On the other hand, resuming routine work after the pandemic has led to a change in the rate of AR in *S. aureus*.

After the pandemic AR in *S. aureus* increased against oxacillin by 37.2%, erythromycin by 13.5%, and vancomycin from 14% to 24%. [47]. During the severe acute respiratory syndrome (SARS) outbreak in 2003, preventive measures were implemented and this resulted in increase in methicillin-resistant *Staphylococcus aureus* (MRSA) [48]. In the current study, resistance of *S. aureus* to most of the tested antibiotics was slightly increased after the pandemic than before and during the pandemic, although it remained 100% sensitive to daptomycin and vancomycin. The findings reported by Iqbal *et al.* are in line with our results, except for vancomycin, in which

they observed an increase in resistance after the pandemic [47].

A previous report noted that resistance of *E. faecium* to ampicillin, ciprofloxacin, and gentamicin decreased after the pandemic [47]. A systematic review during the COVID-19 pandemic reported high resistance of *E. faecium* to ampicillin, ciprofloxacin, and erythromycin [14]. In the current study, the resistance of *E. faecium* increased during the pandemic compared to before and after the pandemic. Resistance to ciprofloxacin, linezolid, teicoplanin, tetracycline, and vancomycin increased during the pandemic, while after the pandemic, the resistance increased against daptomycin and erythromycin. Similarly, studies by Sini *et al*. reported an increased resistance of *E. faecium* to tested antibiotics, including ampicillin, erythromycin, tetracycline, linezolid, high-level gentamicin, and ciprofloxacin [14,33].

A high level of incidence of *E. faecium* was reported during COVID-19 compared to the time before, which was due to increased ICU admission attributable to the pandemic and using prophylactic antibiotics to avoid acquiring Gram-negative bacterial infections [28-29]. Other studies found that *E. faecium* increased during the pandemic among COVID-19 patients who had a longer length of stay, used medical devices, and received empirical therapy [30,49,50]. Greene *et al.* assessed the factors associated with increased AR in *E. faecium* and highlighted immune suppression, recent invasive procedures, and neutropenia as the main factors [31]. Similarly, the present study concluded that the AR of *E. faecium* was increased during COVID-19 compared to before and after COVID-19. The increased AR of *E. faecium* during COVID-19 in our study could be explained by the circumstances during pandemic, where most of the COVID-19 cases needed intubation and medical devices such as central lines and urinary catheters. Some of the cases stayed in the ICU for a long time and were immunocompromised.

Although *A. baumannii* in the current study showed high resistance against amikacin (66-82%) after the pandemic, the overall pattern of AR for Gram-negative bacteria decreased over three years. This is almost in concordance with two previous studies [47,51]. The notable high resistance of *A. baumannii* against amikacin could be explained by the increased consumption of antibiotics during COVID-19. In contrast, previous studies reported an increase in AR among Gram-negative bacteria during and after the COVID-19 pandemic [14,32,33].

There was no major difference in the predominant AR bacteria before, during, and after COVID-19. *E. coli* constituted the most frequent bacterium before the pandemic, followed by *K. pneumonia* and *S. aureus*. It was the same during and after COVID-19, except for *S. aureus*, which became the second most common AR bacteria during the pandemic, and the third most common after the pandemic. This is congruent with a study carried out by Saini *et al.* [33]. Another study focusing on AR during the pandemic reported similar findings for the most common AR bacteria [52]. In contrast, it has been reported in a study that the most frequent MDR bacteria before COVID-19 were *S. aureus*, followed by *K. pneumonia* and *Clostridium difficile*, and after COVID-19 were *K. pneumonia*, followed by *S. aureus* and *A. baumannii* [22].

This study had some limitations. First, a retrospective study design was employed, where some patients had multiple admissions and some of them received antibiotics for other reasons. Thus, such factors did not allow us to include antibiotic consumption variables to assess them by differentiating whether there was an association between AR classification (MDR, XDR, and PDR) and the consumption of antibiotics or identifying the proper uses of antibiotics. Furthermore, it was impossible to include antibiotic consumption variables, which should be considered in further studies. These findings cannot be generalized to the entire population because it was a single center study.

However, this study had the following strengths. First, it addressed AR in relation to the time (before, during, and after) of the COVID-19 pandemic over three calendar years. Second, it addressed the pattern of AR among Gram-positive and Gram-negative patients, the factors associated with AR classification, and the factors associated with the death of patients who had positive AR.

Conclusions

This study demonstrated that the prevalence of PDR during the COVID-19 pandemic was high. The length of stay and time classification were significant predictors for AR classification. The factors associated with death of patients with positive AR were age, nationality, COVID-19 infection, smoking, liver disease, type of bacteria, and number of associated bacteria. As a consequence of the strict implementation of policies provided by the IPC department and the government during COVID-19, resistance of Gram-negative bacteria decreased during and after the pandemic compared to before the pandemic. However,

S. aureus showed negligible resistance after the pandemic, which could be due to the resumption of routine work, and *E. faecium* indicated high resistance during the pandemic, which could be due to factors related to the patients' status. The predominance of AR bacteria did not change substantially. Further studies are recommended to explore the fundamental reasons for the high prevalence of PDR and increased *E. faecium* AR during the COVID-19 pandemic.

Acknowledgements

We would like to thank the administration of King Khalid Hospital for facilitating data collection.

References

1. Andersson DI, Hughes D (2010) Antibiotic resistance and its cost: is it possible to reverse resistance? Nat Rev Microbiol 8: 260-271. doi: 10.1038/nrmicro2319.
2. Devi P, Rodrigues C, Naik CG, D'Souza L (2012) Isolation and characterization of antibacterial compound from a mangrove-endophytic fungus, *Penicillium chrysogenum* MTCC 5108. Indian J Microbiol 52: 617-623. doi: 10.1007/s12088-012-0277-8.
3. Hutchings MI, Truman AW, Wilkinson B (2019) Antibiotics: past, present and future. Curr Opin Microbiol 51: 72-80. doi: 10.1016/j.mib.2019.10.008.
4. Rourke AO, Beyhan S, Choi Y, Morales P, Chan AP, Espinoza JL, Dupont, CL Meyer KJ, Spoering A, Lewis K, Nierman WC, Nelson KE (2020) Mechanism-of-action classification of antibiotics by global transcriptome profile. Antimicrob Agents Chemother 64: 1-15. doi: 10.1128/AAC.01207-19.
5. World Health Organization (2021) Antimicrobial resistance. Available: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. Accessed: 11 January 2023.
6. Nathan C (2004) Antibiotics at the crossroads. Nature 431: 899-902. doi: 10.1038/431899a.
7. Ventola CL (2015) The antibiotic resistance crisis: part 1: causes and threats. Pharmacy and Therapeutics 40: 277-283.
8. Davies J, Davies D (2010) Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev 74: 417-433. doi: 10.1128/MMBR.00016-10.
9. Rousham EK, Unicomb L, Islam MA (2018) Human, animal and environmental contributors to antibiotic resistance in low-resource settings: integrating behavioural, epidemiological and one health approaches. Proc Biol Sci 285: 20180332. doi: 10.1098/rspb.2018.0332.
10. Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, Satta G, Cooke G, Holmes A (2020) Bacterial and fungal coinfection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis 71: 2459-2468. doi: 10.1093/cid/ciaa530.
11. Dudoignon E, Caméléna F, Deniau B, Habay A, Coutrot M, Ressaire Q, Plaud B, Berçot B, Dépret F (2020) Bacterial pneumonia in COVID-19 critically ill patients: a case series. Clin Infect Dis 72: 905-906. doi: 10.1093/cid/ciaa762.
12. Wright GD (1999) Aminoglycoside-modifying enzymes. Curr Opin Microbiol 2: 499-503. doi: 10.1016/S1369-5274(99)00007-7.
13. Tiri B, Sensi E, Marsiliani V, Cantarini M, Priante G, Vernelli C, Martella LA, Costantini M, Mariottini A, Andreani P, Bruzzone P, Suadoni F, Francucci M, Cirocchi R, Cappanera S (2020) Antimicrobial stewardship program, COVID-19, and infection control: spread of carbapenem-resistant *Klebsiella pneumoniae* colonization in ICU COVID-19 patients. What did not work? J Clin Med 9: 1-9. doi: 10.3390/jcm9092744.
14. Al Sulayyim HJ, Ismail R, Al Hamid A, Ghafar NA (2022) Antibiotic resistance during COVID-19: a systematic review. Int J Environ Res Public Health 19: 11931. doi: 10.3390/ijerph191911931.
15. World Health Organisation (2020) Antibiotic resistance. Available: https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance. Accessed: 22 January 2023.
16. Elsayed AA, Darwish SF, Zewail MB, Mohammed M, Saeed H, Rabea H (2021) Antibiotic misuse and compliance with infection control measures during COVID-19 pandemic in community pharmacies in Egypt. Int J Clin Pract 75: 1-11. doi: 10.1111/ijcp.14081.
17. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, Oczkowski S, Levy MM, Derde L, Dzierba A, Du B, Aboodi M, Wunsch H, Cecconi M, Koh Y, Chertow DS, Maitland K, Alshamsi F, Belley-Cote E, Rhodes A (2020) Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Med 46: 854-887. doi: 10.1007/s00134-020-06022-5.
18. Alghamdi S, Berrou I, Aslanpour Z, Mutlaq A, Haseeb A, Albanghali M, Hammad MA, Shebl N (2021) Antimicrobial stewardship programmes in Saudi hospitals: evidence from a national survey. Antibiotics 10: 193. doi: 10.3390/antibiotics10020193.
19. Herawati F, Jaelani AK, Wijono H, Rahem A, Setiasih, Yulia R, Andrajati R, Soemantri D (2021) Antibiotic stewardship knowledge and belief differences among healthcare professionals in hospitals: a survey study. Heliyon 7: e07377. doi: 10.1016/j.heliyon.2021.e07377.
20. Wee LEI, Conceicao EP, Tan JY, Magesparan KD, Amin IBM, Ismail BBS, Toh HX, Jin P, Zhang J, Wee EGL, Ong SJM, Lee GLX, Wang AE-M, How MKB, Tan KY, Lee LC, Phoon PC, Yang Y, Aung MK, Ling ML (2021) Unintended consequences of infection prevention and control measures during COVID-19 pandemic. Am J Infect Control 49: 469-477. doi: 10.1016/j.ajic.2020.10.019.
21. Pérez de la Lastra JM, Anand U, González-Acosta S, López MR, Dey A, Bontempi E, Morales delaNuez A (2022) Antimicrobial resistance in the COVID-19 landscape: is there an opportunity for anti-infective antibodies and antimicrobial peptides? Front Immunol 13: 921483. doi: 10.3389/fimmu.2022.921483.
22. Bentivegna E, Luciani M, Arcari L, Santino I, Simmaco M, Martelletti P (2021) Reduction of multidrug-resistant (MDR) bacterial infections during the COVID-19 pandemic: a retrospective study. Int J Environ Res Public Health 18: 1-8. doi: 10.3390/ijerph18031003.
23. Clinical and Laboratory Standards Institute. (2017). Performance standards for antimicrobial susceptibility testing. CLSI supplement M100, 106-112.
24. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL (2012) Multidrug-resistant,

extensively drug-resistant and pan drug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 18: 268-281. doi: 10.1111/j.1469-0691.2011.03570.x.

25. Bazaid AS, Barnawi H, Qanash H, Alsaif G, Aldarhami A, Gattan H, Alharbi B, Alrashidi A, Al-Soud WA, Moussa S, Alfouzan F (2022) Bacterial coinfection and antibiotic resistance profiles among hospitalised COVID-19 patients. Microorganisms 10: 1-12. doi: 10.3390/microorganisms10030495.
26. World Health Organization. (2022) WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed: 22 January 2023.
27. News AS (2022) Saudi Arabia's COVID-19 press conferences come to an end. Available: https://www.arabnews.com/node/2040816/saudi-arabia. Accessed: 10 December 2022.
28. Hope R, Gerver SM, Mihalkova M, Bion JF, Wilson APR, Chudasama D, Johnson AP (2020) Laboratory surveillance of *Enterococcus* spp. bacteraemia in England, Wales and Northern Ireland: 2017. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/765458/hpr4618_AA_ntrcccs.pdf. Accessed: 22 January 2023
29. Afzal A, Gutierrez VP, Gomez E, Mon AM, Sarmiento M, Khalid A, Polishchuk S, Al-Khateeb M, Yankulova B, Yusuf M, de Castro YS, Pillai A, Venugopal U, Feinstein A, LaFortune A, Sittler D, Hennessy K, Menon V (2022) Bloodstream infections in hospitalized patients before and during the COVID-19 surge in a community hospital in the South Bronx. Int J Infect Dis 116: 43-46. doi: 10.1016/j.ijid.2021.12.349.
30. Bonazzetti C, Morena V, Giacomelli A, Oreni L, Casalini G, Galimberti LR, Bolis M, Rimoldi M, Ballone E, Colombo R, Ridolfo AL, Antinori S (2020) Unexpectedly high frequency of enterococcal bloodstream infections in coronavirus disease 2019 patients admitted to an Italian ICU: an observational study. Critical Care Medicine 49: E31-E40. doi: 10.1097/CCM.0000000000004748.
31. Greene MH, Harris BD, Nesbitt WJ, Watson ML, Wright PW, Talbot TR, Nelson GE (2018) Risk factors and outcomes associated with acquisition of daptomycin and linezolid-nonsusceptible vancomycin-resistant *Enterococcus*. Open Forum Infect Dis 5: ofy185. doi: 10.1093/ofid/ofy185.
32. Bahçe YG, Acer Ö, Özüdoğru O (2022) Evaluation of bacterial agents isolated from endotracheal aspirate cultures of COVID-19 general intensive care patients and their antibiotic resistance profiles compared to pre-pandemic conditions. Microb Pathog 164: 105409. doi: 10.1016/j.micpath.2022.105409.
33. Saini V, Jain C, Singh NP, Alsulimani A, Gupta C, Dar SA, Haque S, Das S (2021) Paradigm shift in antimicrobial resistance pattern of bacterial isolates during the COVID-19 pandemic. Antibiotics 10: 1-11. doi: 10.3390/antibiotics10080954.
34. Aldhwaihi KA, Alsanad SM, Almutiri AH, Aldoihi S (2021) Assessment of antibiotic resistance pattern of bacteria prevalent during COVID-19 pandemic. J Pharm Res Int 33: 117-127. doi: 10.9734/jpri/2021/v33i57A33975.
35. Ukuhor HO (2021) The interrelationships between antimicrobial resistance, COVID-19, past, and future pandemics. J Infect Public Health 14: 53-60. doi: 10.1016/j.jiph.2020.10.018.
36. Pasero D, Cossu AP, Terragni P (2021) Multi-drug resistance bacterial infections in critically ill patients admitted with COVID-19. Microorganisms 9: 1-14. doi: 10.3390/microorganisms9081773.
37. Du X, Xu X, Yao J, Deng K, Chen S, Shen Z, Yang L, Feng G (2019) Predictors of mortality in patients infected with carbapenem-resistant *Acinetobacter baumannii*: a systematic review and meta-analysis. Am J Infect Control 47: 1140-1145. doi: 10.1016/j.ajic.2019.03.003.
38. Zhou H, Yao Y, Zhu B, Ren D, Yang Q, Fu Y, Yu Y, Zhou J (2019) Risk factors for acquisition and mortality of multidrug-resistant *Acinetobacter baumannii* bacteremia. Medicine 98: e14937. doi: 10.1097/MD.0000000000014937.
39. Hariyanto H, Yahya CQ, Cucunawangsih C, Pertiwi CLP (2022) Antimicrobial resistance and mortality. Afr J Infect Dis 16: 13-20. doi: 10.21010/Ajid.v16i2.2.
40. Gandra S, Tseng KK, Arora A, Bhowmik B, Robinson ML, Panigrahi B, Laxminarayan R, Klein EY (2019) The mortality burden of multidrug-resistant pathogens in India: a retrospective, observational study. Clin Infect Dis 69: 563-570. doi: 10.1093/cid/ciy955.
41. Lin TL, Chang PH, Chen IL, Lai WH, Chen YJ, Li WF, Lee IK, Wang CC (2022) Risk factors and mortality associated with multi-drug-resistant Gram-negative bacterial infection in adult patients following abdominal surgery. J Hosp Infect 119: 22-32. doi: 10.1016/j.jhin.2021.09.021.
42. Manyahi J, Kibwana U, Mgimba E, Majigo M (2020) Multi-drug resistant bacteria predict mortality in bloodstream infection in a tertiary setting in Tanzania. PLoS One 15: 1-11. doi: 10.1371/journal.pone.0220424.
43. Kassa GM, Woldetsadik AT, Gelaw YA, Alemayehu TT, Tsegaye AT, Tamirat KS, Akalu TY (2020) Predictors of mortality among multidrug-resistant tuberculosis patients in central Ethiopia; a retrospective follow-up study. Epidemiol Infect 148: e258. doi: 10.1017/S0950268820002514.
44. Ahmed N, Ali Z, Riaz M, Zeshan B, Wattoo JI, Aslam MN (2020) Evaluation of antibiotic resistance and virulence genes among clinical isolates of *Pseudomonas aeruginosa* from cancer patients. Asian Pac J Cancer Prev 21: 1333-1338. doi: 10.31557/APJCP.2020.21.5.1333.
45. Mehta T (2015) Bacteriological profile and drug resistance pattern of isolates of the patients admitted in medical intensive care unit of a tertiary care hospital in Ahmadabad. National J Med R 4: 222-225.
46. Barai L, Fatema K, Haq JA, Faruq MO, Ahsan AA, Morshed MAHG, Hossain MB (1970) Bacterial profile and their antimicrobial resistance pattern in an intensive care unit of a tertiary care hospital of Dhaka. Ibrahim Medical College Journal 4: 66-69. doi: 10.3329/imcj.v4i2.6499.
47. Iqbal S, Hussain SS (2022) Impact of COVID-19 pandemic on antimicrobial resistance pattern; transition from resistivity to susceptibility. GJMBU 17: 6. doi: 10.25259/GJMPBU_8_2022.
48. Yap FHY, Gomersall CD, Fung KSC, Ho PL, Ho OM, Lam PKN, Lam DTC, Lyon DJ, Joynt GM (2004) Increase in methicillin-resistant *Staphylococcus aureus* acquisition rate and change in pathogen pattern associated with an outbreak of severe acute respiratory syndrome. Clin Infect Dis 39: 511-516. doi: 10.1086/422641.
49. Giacobbe DR, Labate L, Tutino S, Baldi F, Russo C, Robba C, Ball L, Dettori S, Marchese A, Dentone C, Magnasco L, Crea

F, Willison E, Briano F, Battaglini D, Patroniti N, Brunetti I, Pelosi P, Bassetti M (2021) Enterococcal bloodstream infections in critically ill patients with COVID-19: a case series. Ann Med 53: 1779-1786. doi: 10.1080/07853890.2021.1988695.

50. Devoe C, Segal MR, Wang L, Stanley K, Madera S, Fan J, Schouest J, Graham-Ojo R, Nichols A, Prasad PA, Ghale R, Love C, Abe-Jones Y, Kangelaris K, Patterson SL, Yokoe DS, Langelier CR (2022) Increased rates of secondary bacterial infections, including enterococcus bacteremia, in patients hospitalized with COVID-19. Infect Control Hosp Epidemiol 43: 1416-1423. doi: 10.1017/ice.2021.391.
51. Wardoyo EH, Suardana IW, Yasa IWPS, Sukrama IDM (2021) Antibiotics susceptibility of *Escherichia coli* isolates from clinical specimens before and during COVID-19 pandemic. Iran J Microbiol 13: 156-160.
52. Mahmoudi H (2020) Bacterial co-infections and antibiotic resistance in patients with COVID-19. GMS Hyg Infect Control 15: 35.

Corresponding author

Noraini Abdul Ghafar, PhD (Epidemiology & Biostatistics)
School of Health Sciences, Universiti Sains Malaysia (Health Campus),
Kubang Kerian 11800, Kelantan, Malaysia.
Tel: 097677837
Fax: 097677515
Email: norainiag@usm.my

Conflict of interests: No conflict of interests is declared.